REMARKS

Upon entry of the foregoing amendment, claims 88-90, 98, 105, 109, 116-119, 160, 163, 164, 167 and 186-199 are pending. Claims 99-104, 106-108, 110-115, 127-130, 138-141, 149-152, 162, 166, 168, 170, 171, 173, 174, 176, 177, 179, 180, 182, 183 and 185 are withdrawn from consideration as being directed to a non-elected invention. Claims 1-87, 91-97, 120-126, 131-137, 142-148, 153-159, 161, 165, 169, 172, 175, 178, 181 and 184 have been previously canceled without prejudice or disclaimer of the canceled subject matter. Applicant maintains the right to file one or more continuation or divisional applications on any canceled subject matter. Claim 88 is amended herein and new claims 186-199 have been added.

Claim 88 is amended to separate out the adjuvant combination, 3D-MPL + IL-12, into new independent claim 186. New claims 186-199 incorporate the adjuvant combination, 3D-MPL + IL-12. Support for new claims 186-199 can be found in claims 88-90, 98, 105, 109, 116-119, 160, 163, 164 and 167, and elsewhere throughout the specification.

Claim Rejections

35 USC § 112, second paragraph

Claims 98, 105, 109, 116-119, 160, 163, 164 and 167 remain rejected because the phrase "derived from" allegedly renders them indefinite. Applicant maintains the position set forth in the June 27, 2005 amendment. Moreover, it is irrelevant that the Examiner considers herself to be "one of skill in the art," because the legal standard is one of *ordinary* skill in the art, and that is an objective standard. *See Ryko Mfg. Co. v. Nu-Star Inc.*, 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991) ("The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry.") The examiner must ascertain what would have been obvious to one of ordinary skill in the art at the time the invention was made, and not to the inventor, a judge, a layman, those skilled in remote arts, or to geniuses in the art at hand. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 218 USPQ 865 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

One of ordinary skill in the art does understand the meaning of "derived from" as evidenced by its usage in numerous issued patents. See June 27, 2005 amendment. Further evidence can be found in the *Dictionary of Biochemistry and Molecular Biology*, p. 506 (John Wiley & Sons, 1989), which defines "vaccine" as a suspension of antigens that are derived from infectious bacteria or viruses and that, upon administration to humans or to animals, will produce active immunity and will provide protection against infection by these, or by related, bacteria or viruses. (Emphasis added.)

In view of the foregoing, Applicant maintains that the rejection under 35 USC 112, second paragraph, is improper and should be withdrawn.

35 USC § 102(a)

Claims 88-90 stand rejected as allegedly being anticipated by Boon et al. (WO 98/57659) in view of Morein et al. (U.S. Patent No. 5,603,958). Applicant traverses this rejection.

The Law of Anticipation

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Brothers Inc. v. Union Oil Co. of Cal.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The law permits, however, the use of extrinsic evidence to interpret or explain the disclosure of a prior art reference whose anticipatory effect is otherwise ambiguous. *See Studiengesellschaft Kohle, m.b.H. v. Dart Industries, Inc., 220 USPQ 841, 842* (Fed. Cir. 1984). Such evidence may only be used to explain the meaning the reference would have had to the person of ordinary skill in the art, but may not be used to expand or fill gaps in the teachings of the reference.

Anticipation under 35 USC 102(a) requires that the *same invention*, including each element and limitation of the claims, was known or used by others *before* the patentee invented it. *Hoover Group Inc. V. Custom Metalcraft Inc.*, 36 USPQ2d 1101, 1103 (Fed. Cir. 1995).

The Claimed Invention

Claim 88 as amended is directed to an antigenic composition consisting of an antigen and an effective *adjuvanting* amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) granulocyte macrophage colony stimulating factor (GM-CSF), together with a diluent or carrier. New independent claim 186, carved out of original claim 88, is directed to an antigenic composition consisting of an antigen and an effective *adjuvanting* amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) interleukin-12 (IL-12), together with a diluent or carrier. In short, the present invention requires the use of a two-adjuvant composition (3D-MPL + GM-CSF or 3D-MPL + IL-12), an antigen from a pathogenic virus, and a carrier.

The Primary Reference

Boon et al., on the other hand, disclose an adjuvant composition comprising a mixture of not less than three adjuvants: a saponin adjuvant, monophosphoryl lipid A or a derivative thereof, and IL-12. In particular, Boon et al.'s adjuvant composition comprises 3 de-o-acylated monophosphoryl lipid A (3D-MPL), the saponin adjuvant QS21, and IL-12. (Page 1, lines 4-8; page 2, lines 20-29; claims 1-3). Boon et al.'s composition does not contain GM-CSF because they found that it was "unable to enhance the effect of the QS21/MPL adjuvant." (Page 3, lines 16-17).

The Extra Reference

QS-21 is clearly and unambiguously used as an adjuvant in Boon et al.'s adjuvant composition. A person of ordinary skill in the art reading Boon et al. would have no reason to question this. Nonetheless, the Examiner takes the position that Boon et al.'s QS-21 is a carrier, citing the Abstract of Morein et al. (U.S. Patent No. 5,603,958) as supportive. "The carrier that Boon et al. teaches is QS-21. QS-21 is a saponin. Saponins are recognized in the art as a pharmaceutical carrier, as evidenced by Morein et al. [Abstract of Morein et al.] Ergo, Boon et al. teaches a composition consisting of an antigen, 3D-MPL, IL-12, and a carrier." (Office Action, p. 5).

Reading the Morein '958 patent in its entirety clarifies that the pharmaceutical carrier of that invention is not a saponin *per se*. Rather, the carrier is an inert, structure-giving, deadjuvanted matrix of a complex of a sterol and one or more saponins that lack

adjuvant effect. "[M]atrix=carrier refers to a structure giving complex between one or more saponins and cholesterol . . . ." (Col. 2, lines 45-46). "The present invention refers to the use [of] an inert, structure giving deadjuvanted matrix of a complex of a sterol, such as cholesterol, and one or more saponins[,] as a carrier for the administration of a drug, which matrix has an annular basic structure which can form spherical nano particles having a narrow size distribution." (Col. 2, lines 57-62). And claim 1 recites a method of administering a pharmaceutically active substance in a carrier, wherein the carrier comprises a deadjuvanted matrix, which is a complex of a sterol and one or more saponins that lack adjuvant effect.

The Morein '958 patent further clarifies that Quil A, a crude saponin mixture, "can be divided into different substances, *inter alia* B2, B3 and B4b, some of which show adjuvant effect and others giving a structure effect." (Col. 2, lines 11-15). The saponins used in the Morein '958 patent for the deadjuvanted carrier matrix are the structure-forming saponins, (col. 3, lines 28-29), such as, for example, B4b, a mixture of B4b and B2, LT15 and LT17 (col. 3, lines 35-44; col. 4, lines 19-21) . That these saponins lack adjuvant activity is exemplified and confirmed by the biological test performed in mice, which is disclosed in col. 13, lines 1-39. The result shown in Table 6 demonstrates that LT15 (an adjuvant depleted fraction of Quil A) as well as plain saline did not potentiate the antibody response to the protein micelles in contrast to the non-depleted Quil A preparation.

In contrast, QS-21 is known by one of ordinary skill in the art as a substantially pure saponin characterized as having immune adjuvant activity. See U.S. Patent No. 5,057,540 cited in the supplemental IDS that accompanies this amendment. Boon et al. explicitly discloses that QS-21 is a saponin *adjuvant* and cites the '540 patent as well. See page 2, line 28. Since the saponins in Morein et al.'s carrier matrix lack adjuvant activity, they do not include QS-21.

The Examiner's reliance on the Morein '958 patent to interpret the allegedly anticipating Boon et al. reference is misplaced. The Examiner relies on the Morein '958 patent for "a very specific teaching", not otherwise present in the Boon et al. reference. Therefore, the combination of these references cannot anticipate the claimed invention. *Studiengesellschaft Kohle*, 220 USPQ at 842.

Furthermore, contrary to the Examiner's assertion that Boon et al. would have necessarily had the composition comprising an antigen, 3D-MPL, GM-CSF and a carrier,

even though Boon et al. point out that GM-CSF was unable to enhance the effect of the QS-21/MPL adjuvant, this adjuvant composition, i.e., 3D-MPL/GM-CSF/QS-21, is not Applicant's composition.

Again, Boon et al.'s invention provides for a three-adjuvant composition comprising QS-21, 3D-MPL and IL-12; Applicant's invention provides for an antigenic composition consisting of an antigen, a two-adjuvant composition consisting of 3D-MPL + GM-CSF or 3D-MPL + IL-12, and a carrier. One of ordinary skill in the art would understand that Applicant's carrier is not a third adjuvant, but merely a vehicle, such as an injectable liquid, for facilitating administration of the active ingredient. And the Examiner is reminded that Applicant is not required to teach that which is well known to one of ordinary skill in the art.

Since every element of the presently claimed invention is not identically shown in Boon et al., the claimed invention cannot be anticipated by this reference. Applicant therefore requests that this rejection be withdrawn.

35 USC § 103(a)

1. Claims 98, 116, 117 and 119 stand rejected as being obvious over Boon et al., WO 98/57659, as applied to claims 88 and 90 above. Applicant traverses the rejection.

Claim 88 as amended is directed to an antigenic composition consisting of an antigen and an effective adjuvanting amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) GM-CSF, together with a diluent or carrier. The dependent claims recite that the antigen is derived from a pathogenic virus (claim 98), particularly HIV (claims 116-117), and that the 3D-MPL in the composition of claim 116 is used in the form of a stable oil-in-water emulsion (claim 119).

New independent claim 186, carved out of original claim 88, is directed to an antigenic composition consisting of an antigen and an effective *adjuvanting* amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) IL-12, together with a diluent or carrier. The dependent claims recite that the antigen is derived from a pathogenic virus (claim 189), particularly HIV (claims 192-193), and that the 3D-MPL in the composition of claim 192 is used in the form of a stable oil-in-water emulsion (claim 195).

In short, the present invention requires the use of a two-adjuvant composition (3D-MPL + GM-CSF or 3D-MPL + IL-12), an antigen from a pathogenic virus, and a carrier.

In contrast, Boon et al. are concerned with identifying the cytokine that would best augment the already known adjuvant combination of MPL and the saponin adjuvant QS-21. Throughout the disclosure, Boon et al. refer only to a three-adjuvant combination that contains IL-12, MPL and QS-21. Boon et al. do not teach that GM-CSF is a possible component of the adjuvant combination. Rather, Boon et al. teach that GM-CSF was "unable to enhance the effect of the QS21/MPL adjuvant." (Page 3, lines 16-17). As such, Boon et al. teach away from the presently claimed invention.

The Examiner insists that QS-21 is a carrier when Boon et al. clearly state that QS-21 is a saponin adjuvant. Boon et al. even cite U.S. Patent No. 5,057,540 ("Saponin Adjuvant"), which discloses that QS-21 is a substantially pure saponin having immune adjuvant activity (Col. 6, lines 33-34). The Examiner's reliance on the Morein '958 patent is again misplaced because the saponins used in the carrier matrix provide a structure-giving effect, not an adjuvant effect, and therefore, do not include QS-21.

Furthermore, contrary to the Examiner's assertion that Boon et al. would have *necessarily* had the composition comprising an antigen, 3D-MPL, GM-CSF, and a carrier, that which is inherent in the prior art, if not known at the time of the invention, cannot form a proper basis for rejecting the claimed invention as obvious under section 103. *See In re Shetty*, 195 USPQ 753, 756-57 (CCPA 1977).

Moreover, motivation would be lacking when the state of the art at the time of the invention in question was discovered pointed researchers in a different direction than the inventor proceeded. Indeed, the Federal Circuit has repeatedly recognized that proceeding contrary to the accepted wisdom in the art represents "strong evidence of non-obviousness." *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986); W.L. Gore & Assocs., Inc. v. Garlock, Inc., 220 USPQ 303, 312 (Fed. Cir. 1983), *cert denied,* 469 U.S. 851 (1984) (prior art teaching that conventional polypropylene should have reduced crystallinity before stretching and should undergo slow stretching, led away from claimed process of producing porous article by expanding highly crystalline PTFE by rapid stretching); *accord In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988).

Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness, and therefore, requests that this rejection be withdrawn.

2. Claims 105, 109, 160, 163, 164 and 167 stand rejected as being obvious over Boon et al., WO 98/57659, as applied to claims 88, 98 and 116 above. Applicant traverses the rejection.

Claims 105, 109, 160, 163, 164 and 167 depend directly or indirectly from independent claim 88. Claim 88 as amended is directed to an antigenic composition consisting of an antigen and an effective adjuvanting amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) GM-CSF. Dependent claims 105, 160 and 163 recite the administration of the antigenic composition of claim 98 (wherein the antigen is from a pathogenic virus) to a vertebrate host to elicit an immune response in the host. Dependent claims 109, 164 and 167 recite the administration of the antigenic composition of claim 98 to a vertebrate host to elicit cytotoxic T lymphocyte responses in the host.

New independent claim 186, carved out of original claim 88, is directed to an antigenic composition consisting of an antigen and an effective *adjuvanting* amount of the combination of: (1) 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A, and (2) IL-12, together with a diluent or carrier. Dependent claims 190, 196 and 197 recite the administration of the antigenic composition of claim 189 (wherein the antigen is from a pathogenic virus) to a vertebrate host to elicit an immune response in the host. Dependent claims 191, 198 and 199 recite the administration of the antigenic composition of claim 189 to a vertebrate host to elicit cytotoxic T lymphocyte responses in the host.

As Applicant pointed out above, Boon et al. disclose an adjuvant composition comprising not less than three adjuvants: a saponin adjuvant, monophosphoryl lipid A or a derivative thereof, and IL-12. In particular, Boon et al.'s adjuvant composition comprises QS21, 3-O-deacylated monophosphoryl lipid A (3D-MPL), and IL-12. Boon et al.'s composition would not contain GM-CSF because they found that it was "unable to enhance the effect of the QS21/MPL adjuvant." Therefore, the skilled artisan who combines Boon et al.'s three-adjuvant composition with an antigen to elicit an immune response or cytotoxic T lymphocyte responses does not arrive at the present invention as claimed, which requires the use of a two-adjuvant composition (3D-MPL + GM-CSF or 3D-MPL + IL-12), an antigen from a pathogenic virus, and a carrier.

The rejection is improper and should be withdrawn.

3. Claim 118 stands rejected as being obvious over Boon et al., WO 98/57659, in view of Haynes et al., U.S. Patent No. 5,993,819 ("the Haynes '819 patent"), as being applied to claims 88, 98, 116 and 117 above. Applicant traverses the rejection.

Claim 118, which depends indirectly from claim 88 provided above, recites that the antigen is the HIV peptide having the amino acid sequence of either SEQ ID NO:1 or SEQ ID NO:2.

Contrary to the Examiner's assertion that Boon et al. teach an antigenic composition consisting of an antigen together with a specific two-adjuvant composition, Boon et al. explicitly discloses and claims an adjuvant composition comprising no less than three adjuvants: a saponin adjuvant, monophosphoryl lipid A or a derivative thereof, and IL-12. QS-21 is the preferred saponin adjuvant; it is not used as a carrier, i.e., a vehicle, as Applicant has claimed.

The Examiner's misinterpretation of the art - art that is unambiguous - to deny Applicant's right to the claimed invention flies in the face of Article I, § 8, cl. 8 of the U.S. Constitution, the purpose of which is to *promote* the progress of useful arts, by securing for limited times to inventors the exclusive right to their discoveries. The Examiner's reliance on the Morein '958 patent for every rejection is a blatant error and contrary to settled law. Applicant's claimed invention is not *prima facie* obvious.

Conclusion

In conclusion, this amendment and reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.

Respectfully submitted,

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V

v Reaction rate.

v_0 1. Initial velocity. 2. Control velocity; initial velocity in the absence of an inhibitor.

$\bar{v}$ Partial specific volume.

V 1. Maximum velocity. 2. Volume. 3. Volt. 4. Valine. 5. Vanadium.

vacant lattice point model A model for the structure of water according to which the water structure is an essentially crystalline system that is closely related to an open, expanded, ice-like structure into which free and nonassociated water molecules can easily fit.

vaccenic acid An unsaturated fatty acid that contains 18 carbon atoms and one double bond; it is the major unsaturated fatty acid in *E. coli*.

vaccination An immunization in which a vaccine is administered to humans or to animals for the purpose of establishing resistance to an infectious disease.

vaccine A suspension of antigens that are derived from infectious bacteria or viruses and that, upon administration to humans or to animals, will produce active immunity and will provide protection against infection by these, or by related, bacteria or viruses.

vaccinia virus A virus of the poxvirus group that infects humans and many animals.

vacuole An intracellular structure, surrounded by a single membrane (tonoplast) and filled with fluid. Plant vacuoles are usually large and occupy a major portion of the cell volume. Animal vacuoles are much smaller and are also known as secretory vesicles or secretory granules.

vacuolysosome A lysosome that has fused with a vacuole.

vacutainer An evacuated tube used in the drawing of blood.

vacuum evaporator A vacuum chamber in which metal atoms are evaporated in the process of shadowcasting specimens for electron microscopy.

vacuum ultraviolet The range of the ultraviolet spectrum that encompasses wavelengths less than 1.8×10^{-5} cm.

Val 1. Valine. 2. Valyl.

valence 1. The number of electrons of an atom or a group of atoms that participate in the formation of chemical bonds. 2. ANTIGEN VALENCE. 3. ANTIBODY VALENCE.

valence bond theory The theory of chemical bonding that is developed by considering the atoms to have intact atomic orbitals, and then moving the atoms closer to each other with a resultant overlap of the atomic orbitals. According to this theory, a covalent bond is formed by the overlap of two orbitals, one from each bonding atom, and with each orbital holding one electron. A coordinate covalent bond is formed by the overlap of an orbital of one atom, holding two electrons, with an unoccupied orbital of a second atom.

valence electron An electron that is located in the outermost energy shell of an atom and that participates in the formation of chemical bonds.

valency Variant spelling of valence.

-valent Combining form meaning valence; used either with mono, di, ..., poly to indicate the chemical valence of atoms and ions, or with uni, bi, ..., multi to indicate the immunological valence of antigens or antibodies.

valine An aliphatic, branched, nonpolar alpha amino acid that contains five carbon atoms. *Abbr* Val; V.

valinemia A genetically inherited metabolic defect in humans due to a deficiency of the enzyme valine aminotransferase.

valinomycin An ionophorous antibiotic, produced by *Streptomyces fulvissimus*, that acts as an uncoupler of oxidative phosphorylation; a depsipeptide antibiotic.

vanadium An element that is essential to humans and animals. Symbol, V; atomic number, 23; atomic weight, 50.942; oxidation states, +2, +3, +4, +5; most abundant isotope, ^{51}V; a radioactive isotope, ^{48}V, half-life, 16 days, radiation emitted, positrons and gamma rays.

vancomycin A glycopeptide antibiotic, produced by some species of *Actinomycetes*, that inhibits peptidoglycan biosynthesis.

van Deemter equation An equation that expresses the height equivalent of a theoretical plate in chromatography as the sum of three terms: an eddy diffusion term, a molecular diffusion term, and a mass transfer term.

van Deemter plot A plot of height equivalent of a theoretical plate as a function of average gas flow rate in a gas chromatographic column.

van den Bergh reaction A colorimetric reaction for bilirubin that is based on the formation of

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